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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,718	02/12/2002	Allan Y. Chen	693243-76 (UCD-1120)	1621

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	7

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,718	CHEN, ALLAN Y.	
	Examin r	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group II, claims 23-33 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that while the claims within each group of claims are independent and patentably distinct from the claims of another group, the claims are directed to methods of using indolocarbazole derivatives having the recited structure A to treat neoplastic cells and they are closely related. This is not persuasive because as Applicant's acknowledgment that the inventions are independent and patentably distinct and the examination of both independent and distinct invention, especially the required non-patent literature search would place burden on the Examiner. Therefore, the restriction requirement sent on last Office Action is deemed proper and made final. Accordingly, claims 1-22 are withdrawn from consideration since they are non-elected invention.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 23-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of a neoplastic growth of **breast**

cancer", does not reasonably provide enablement for the "treating a neoplastic growth". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating a neoplastic growth comprising administrating an indolocarbazole derivative having the structure A and radiation. The nature of the invention is extremely complex in that it encompasses the actual treatment of any neoplastic growth such that the subject treated with above structures does not develop a neoplastic growth.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass to a method of treating a complex cell proliferation in need of such treatment which has potentially many different causes (i.e. many different mutations or combination of

mutations). Each of which may or may not be addressed by the administration of the claimed combination.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually treat any neoplastic growth is minimal. All of the guidance provided by the specification is directed towards treatment related to neoplastic growth of breast cancer rather than treatment of any neoplastic growth.

Working Examples: All of the working examples provided by the specification are directed toward the treatment related to neoplastic growth of breast cancer rather than treatment of any neoplastic growth.

State of the Art: While the state of the art is relatively high with regard to treatment of cell proliferation disorders (i.e. specific cancer), the state of the art with regard to treatment of any neoplastic growth is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a structure similar to the claimed structure was administered to a subject to treat development of any neoplastic growth.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of any neoplastic growth in a subject with the claimed structures in combination makes practicing the claimed invention unpredictable in terms of treating any neoplastic growth.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of

appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed structures in combination with radiation and test the combination in the model system to determine whether or not the combination is effective for treating any neoplastic growth. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to treatment of any neoplastic growth with any combination, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding treating a neoplastic growth with any combination, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any neoplastic growth in a subject by administration of one of the claimed combination.

Therefore, a method of treating a neoplastic growth comprising administering combination comprising structure A is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (1997) in view of Prudhomme (2000).

Chen et al. teach that the role of DNA topoisomerase I as a biochemical mediator of radiosensitization in cultured mammalian cells by campotothecain derivatives and it was found that campotothecin enhanced the cytotoxicity of radiation in a schedule-dependent manner by interaction with DNA topoisomerase I. Chen et al. also teach that DNA topoisomerase I, the major cytotoxic target of camptothecin derivatives, was proposed to play a pivotal role in inducing radiosensitization in cells. Chen et al. also demonstrated that mammalian DNA topoisomerase I mediated the enhancement of radiation cytotoxicity. Chen et al. suggest a potential development of topoisomerase I drugs as radiosensitizer in treating human malignancies. Chen et al. teach that the combination of chemotherapy and radiation therapy has become the treatment of choice

for a number of advanced human malignancies. Chen et al. teach that a number of chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation.

Prudhomme teaches that rebeccamycin analogues are an antitumor agent and they inhibit the activity of topoisomerase. Prudhomme teaches that rebeccamycin analogues exhibit potent inhibitory potencies against topoisomerase I.

The primary reference does not teach the rebeccamycin analogues in combination with radiation.

It would have been obvious to one of ordinary skill in the art to replace rebeccamycin analogues in place of campotothecin because that rebeccamycin analogues are antitumor agent and they too inhibit the activity of topoisomerase like campotothecin. One of ordinary skill in the art would have been motivated to make such a modification with reasonable expectation of success to provide enhanced cytotoxicity of radiation in with rebeccamycin analogue posing same mechanism as campotothecain (i.e. topoisomerase I inhibition) which is pivotal in enhancement of radiation cytoxicity. Absent any evidence to contrary, there would have been reasonable expectation of successfully treating neoplastic growth comprising administration of rebeccamycin and radiation since the combination of chemotherapy and radiation therapy has become the treatment of choice for a number of advanced human malignancies and a number of chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation as taught by Chen et al. Further, there is a suggestion of a potential development of topoisomerase I drugs as

radiosentizier in treating human malignancies by Chen et al. One of ordinary skill in the art would have been motivated to employ a potent topoisomerase I drug such as rebeccamycin with radiation in treating human malignancies in a method taught by Chen et al. The amounts of active agents to be used at a noncytotoxic level is obvious because the combination of topoisomerase inhibitor I and radiation treatment provided enhanced cytotoxicity effect as taught by Chen et al. One of ordinary skill in the art would be motivated to use reduced amounts of the active agent to avoid unnecessary extra dosage of potent chemotherapeutic agents. For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 703-308-2232. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 703-305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

THEODORE J. CRIARES
PRIMARY EXAMINER
GROUP 1200

Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

jmk
October 16, 2003